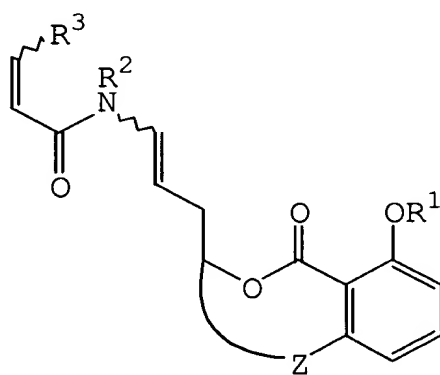


CLAIMS

1. (Currently Amended) A method of treating ~~or preventing a~~ an intra-organellar acidification of intracellular organelles condition treatable by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase, said method comprising administering to a patient an amount effective to treat intra-organellar acidification of intracellular organelles of a vacuolar-type (H<sup>+</sup>)-ATPase ~~inhibiting effective amount~~ of at least one compound of the formula:

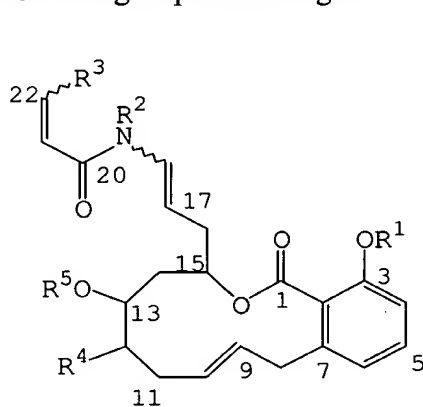


(I),

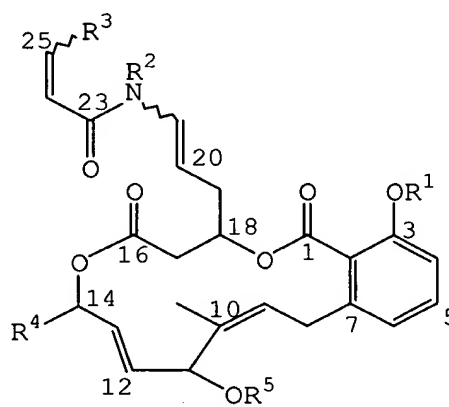
wherein R<sup>1</sup> and R<sup>2</sup> are the same or different and each is H, a straight-chain or branched saturated or unsaturated alkyl, an aryl, R<sup>6</sup>CH<sub>2</sub>-, R<sup>6</sup>CO-, or R<sup>6</sup>SO<sub>2</sub>-, wherein R<sup>6</sup> is H, a straight-chain or branched saturated or unsaturated alkyl, or an aryl; R<sup>3</sup> is H, a straight-chain or branched saturated or unsaturated alkyl, an aryl, an oxime, or an oxime methyl ether; the aromatic ring is unsubstituted or substituted with at least one substituent selected from the group consisting of a halogen, a nitro, an amino, a hydroxyl, a thio, an acyl, an alkyl, and a cyano; the saturated alkyl, unsaturated alkyl and aryl substituents defined in R<sup>1</sup>-R<sup>3</sup> and R<sup>6</sup> are unsubstituted or substituted with at least one substituent selected from the group consisting of a halogen, a nitro, an amino, a hydroxyl, a thio, an acyl, an alkyl, and a cyano; and Z is a contiguous linker comprising a chain of ~~0-12~~ 7-10 atoms which, together with the five atoms beginning with the carbon of the aromatic ring of formula (I) in meta-relationship with OR<sup>1</sup> and ending with the carbon directly attached to the alkyl oxygen of the lactone of formula (I), said carbons being covalently bonded to either end of linker Z, integrally form a ~~5-17~~ 12-15 membered ring; or a pharmaceutically acceptable salt, an ester, or a prodrug thereof, ~~provided that the condition is not cancer.~~

2. (Currently Amended) The method of claim 1, wherein Z is a contiguous linker comprising a chain of 7-12 ~~10~~ atoms which, together with the five atoms beginning with the carbon of the aromatic ring of formula (I) in meta-relationship with OR<sup>1</sup> and ending with the carbon directly attached to the alkyl oxygen of the lactone of formula (I), said carbons being covalently bonded to either end of linker Z, integrally form a 12-17 ~~15~~ membered ring.

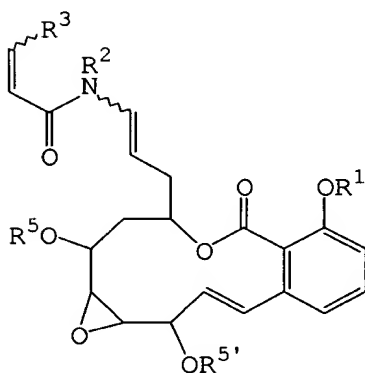
3. (Previously Presented) The method of claim 1, wherein said compound is selected from the group consisting of:



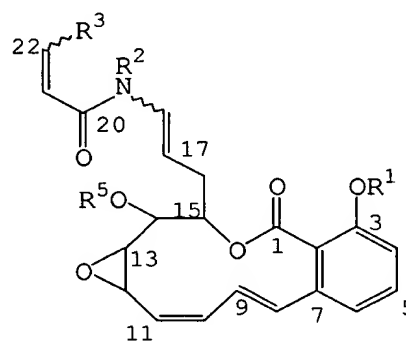
(IA),



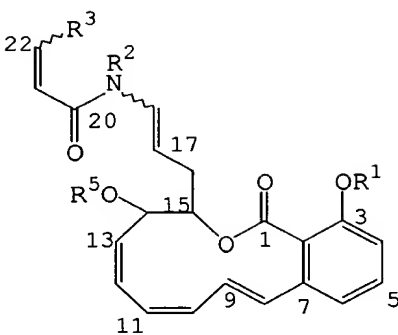
(IB),



(IC),



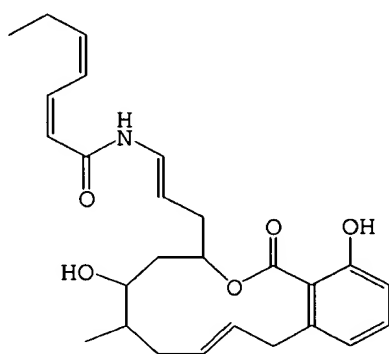
(ID),



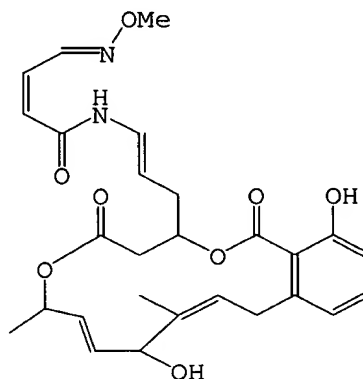
and (IE),

wherein  $R^1$  and  $R^2$  are the same or different and each is H, a straight-chain or branched saturated or unsaturated alkyl, an aryl,  $R^6CH_2-$ ,  $R^6CO-$ , or  $R^6SO_2-$ , wherein  $R^6$  is H, a straight-chain or branched saturated or unsaturated alkyl, or an aryl;  $R^3$  is H, a straight-chain or branched saturated or unsaturated alkyl, an aryl, an oxime, or an oxime methyl ether;  $R^4$  is H, an alkyl, or  $R^7CH_2-$ , wherein  $R^7$  is  $R^6O-$ ,  $R^6CO_2-$ , or  $R^6SO_3-$ ;  $R^5$  and  $R^{5'}$  are the same or different and each is H, a straight-chain or branched saturated or unsaturated alkyl, an aryl, a glycoside,  $R^6CH_2-$ ,  $R^6CO-$ , or  $R^6SO_2-$ ; the saturated alkyl, unsaturated alkyl and aryl defined in  $R^1$ - $R^3$ ,  $R^5$ ,  $R^{5'}$  and  $R^6$ , and the alkyl defined in  $R^4$ , are unsubstituted or substituted with at least one substituent selected from the group consisting of a halogen, a nitro, an amino, a hydroxyl, a thio, an acyl, an alkyl, and a cyano; and the aromatic ring of formula (I) is unsubstituted or substituted with at least one substituent selected from the group consisting of a halogen, a nitro, an amino, a hydroxyl, a thio, an acyl, an alkyl, and a cyano; or a pharmaceutically acceptable salt, an ester, or a prodrug thereof.

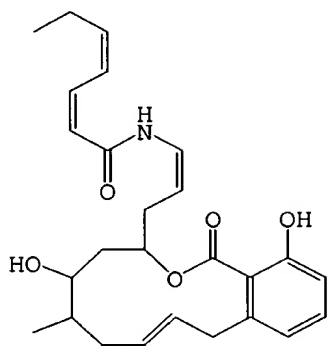
4. (Previously Presented) The method of claim 3, wherein said compound is selected from the group consisting of:



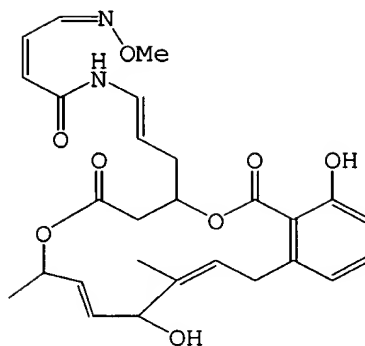
salicylihalamide A,



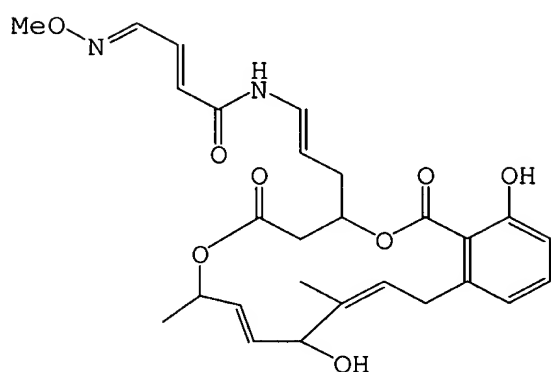
lobatamide A,



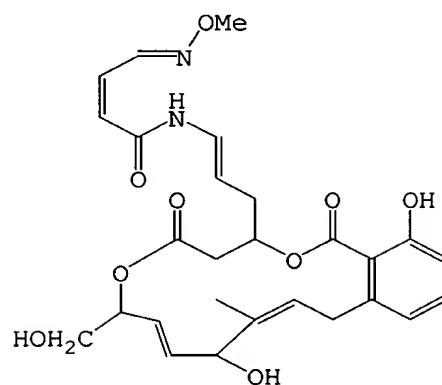
salicylhalamide B,



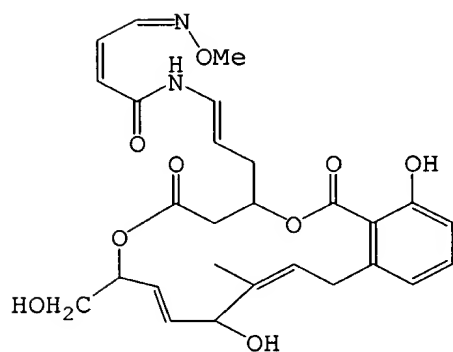
lobatamide B,



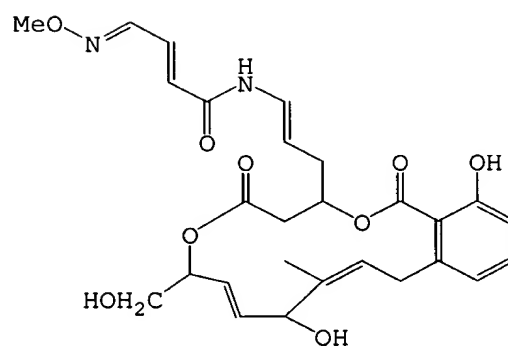
lobatamide C,



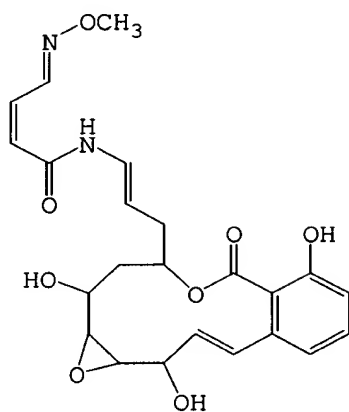
lobatamide D,



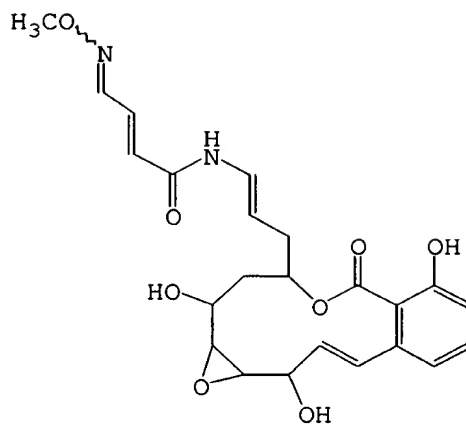
lobatamide E,



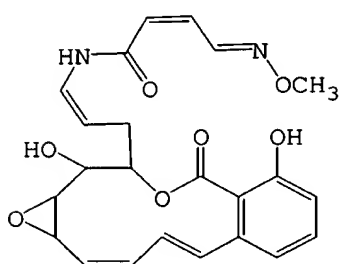
lobatamide F,



CJ-12,950,

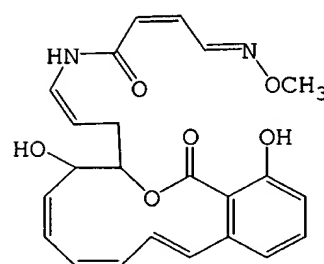


CJ-13,357,



oximidine 1,

and

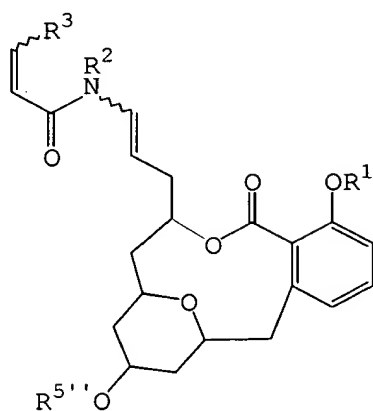


oximidine 2;

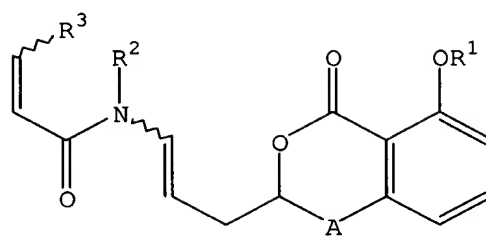
or a pharmaceutically acceptable salt, an ester, or a prodrug thereof.

5. (Currently Amended) The method of claim 1, wherein Z is a contiguous linker comprising a chain of ~~0-6~~ 7-10 atoms which, together with the five atoms beginning with the carbon of the aromatic ring in meta-relationship with OR<sup>1</sup> and ending with the carbon directly attached to the alkyl oxygen of the lactone, said carbons being covalently bonded to either end of linker Z, integrally form a ~~5-11~~ 12-15 membered ring.

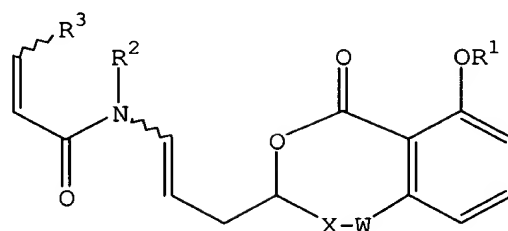
6. (Currently Amended) ~~The method of claim 1, wherein said compound is selected from the group consisting of~~ A method of treating an intra-organellar acidification of intracellular organelles by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase, said method comprising administering to a patient an amount effective to treat intra-organellar acidification of intracellular organelles of a vacuolar-type (H<sup>+</sup>)-ATPase of at least one compound of the formula:



(IF),



(IG)

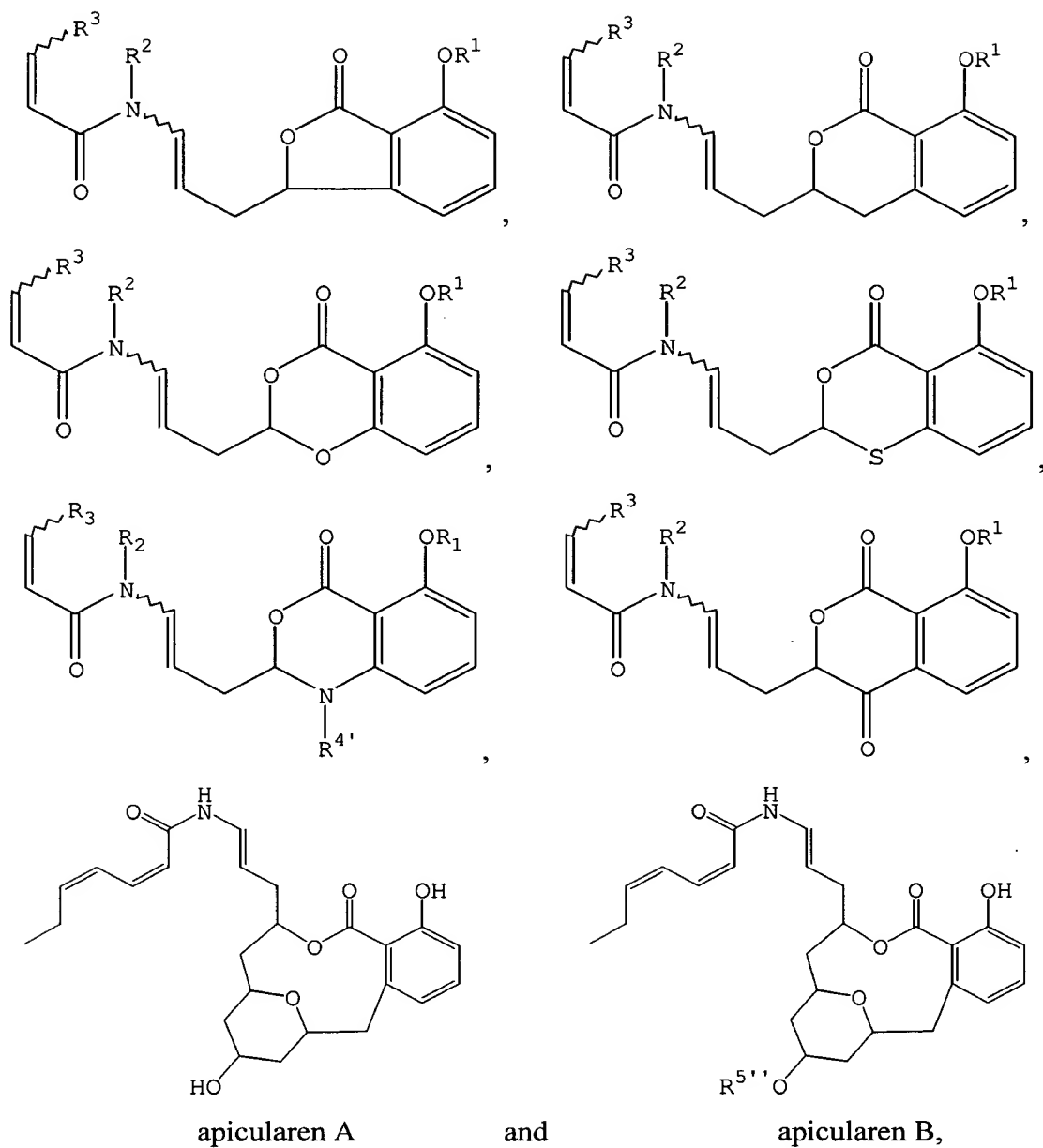


and

(IH),

wherein R<sup>1</sup>-R<sup>3</sup> are as defined in claim 1; R<sup>5''</sup> is H, a straight-chain or branched saturated or unsaturated alkyl, an aryl, a glycoside, R<sup>6</sup>CH<sub>2</sub>-, R<sup>6</sup>CO-, or R<sup>6</sup>SO<sub>2</sub>-, wherein R<sup>6</sup> is as defined in claim 1; the saturated alkyl, unsaturated alkyl and aryl defined in R<sup>5''</sup> are unsubstituted or substituted with at least one substituent selected from the group consisting of a halogen, a nitro, an amino, a hydroxyl, a thio, an acyl, an alkyl, and a cyano; A is a covalent bond or a C<sub>1</sub>-C<sub>6</sub> straight-chain saturated or unsaturated alkyl linker which is unsubstituted or is substituted with a one or more substituents selected from the group consisting of a halogen, a nitro, an amino, a hydroxyl, a thio, an acyl, an alkyl, and a cyano; X is a covalent bond or a C<sub>1</sub>-C<sub>5</sub> straight-chain saturated or unsaturated alkyl linker which is unsubstituted or is substituted with a one or more substituents selected from the group consisting of a halogen, a nitro, an amino, hydroxyl, thio, acyl, C<sub>1</sub>-C<sub>6</sub> alkyl, and cyano; and W is O, S, C(O), C(S), S(O)<sub>n</sub> or N-R<sup>4'</sup>, wherein R<sup>4'</sup> is H, C<sub>1</sub>-C<sub>6</sub> straight-chain or branched saturated or unsaturated alkyl, aryl, R<sup>6</sup>CH<sub>2</sub>-, R<sup>6</sup>CO-, or R<sup>6</sup>SO<sub>2</sub>-, R<sup>6</sup> is as defined in claim 1, and n is an integer from 0-2.

7. (Previously Presented) The method of claim 6, wherein said compound is selected from the group consisting of:



wherein R<sup>5''</sup> is N-acetyl-β-D-glucosamine.

8. (Currently Amended) The method of claim 1, which further comprises co-administering to a patient in need thereof a therapeutically effective amount of at least one additional compound other than a compound defined in ~~any~~ of claim 1.

9. (Previously Presented) The method of claim 8, wherein said additional compound is selected from the group consisting of bafilomycins and concanamycins.

10. (Previously Presented) The method of claim 9, wherein said additional compound is concanamycin A.

11. (Previously Presented) The method of claim 9, wherein said additional compound is bafilomycin A<sub>1</sub>.

12. (Previously Presented) The method of claim 1, wherein said vacuolar-type (H<sup>+</sup>)-ATPase inhibiting-effective amount is effective to inhibit intra-organellar acidification of intracellular organelles.

13. (Previously Presented) The method of claim 1, wherein said vacuolar-type (H<sup>+</sup>)-ATPase inhibiting-effective amount is effective to inhibit urinary acidification.

14. (Previously Presented) The method of claim 1, wherein said vacuolar-type (H<sup>+</sup>)-ATPase inhibiting-effective amount is effective to inhibit bone resorption.

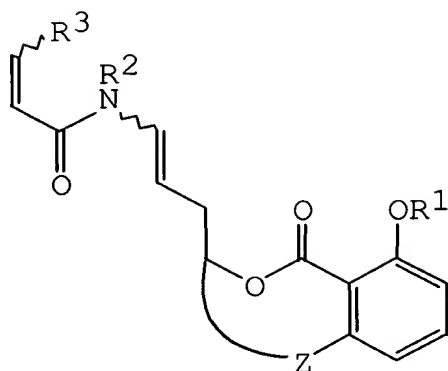
15. (Previously Presented) The method of claim 14, wherein said vacuolar-type (H<sup>+</sup>)-ATPase inhibiting-effective amount is effective to treat osteoporosis.

16. (Previously Presented) The method of claim 1, wherein said vacuolar-type (H<sup>+</sup>)-ATPase inhibiting-effective amount is effective to inhibit fertility.

17. (Previously Presented) The method of claim 1, wherein said vacuolar-type (H<sup>+</sup>)-ATPase inhibiting-effective amount is effective to inhibit angiogenesis.

18. (Previously Presented) A composition comprising a vacuolar-type (H<sup>+</sup>)-ATPase inhibiting-effective amount of at least one compound of the formula:

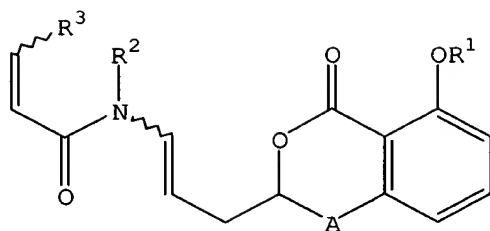




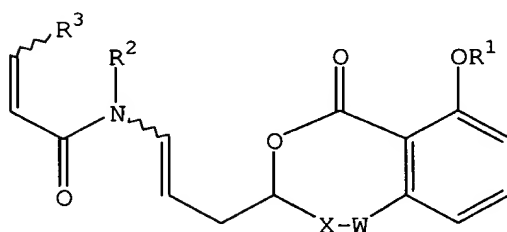
(I) ,

wherein R<sup>1</sup> and R<sup>2</sup> are the same or different and each is H, a straight-chain or branched saturated or unsaturated alkyl, an aryl, R<sup>6</sup>CH<sub>2</sub>-, R<sup>6</sup>CO-, or R<sup>6</sup>SO<sub>2</sub>-, wherein R<sup>6</sup> is H, a straight-chain or branched saturated or unsaturated alkyl, or an aryl; R<sup>3</sup> is H, a straight-chain or branched saturated or unsaturated alkyl, an aryl, an oxime, or an oxime methyl ether; the saturated alkyl, unsaturated alkyl and aryl substituents defined in R<sup>1</sup>-R<sup>3</sup> and R<sup>6</sup> are unsubstituted or substituted with at least one substituent selected from the group consisting of a halogen, a nitro, an amino, a hydroxyl, a thio, an acyl, an alkyl, and a cyano; the aromatic ring is unsubstituted or substituted with at least one substituent selected from the group consisting of a halogen, a nitro, an amino, a hydroxyl, a thio, an acyl, an alkyl, and a cyano; and Z is a contiguous linker comprising a chain of 0-6 atoms which, together with the five atoms beginning with the carbon of the aromatic ring of formula (I) in meta-relationship with OR<sup>1</sup> and ending with the carbon directly attached to the alkyl oxygen of the lactone of formula (I), said carbons being covalently bonded to either end of linker Z, integrally form a 5-11 membered ring; or a pharmaceutically acceptable salt, an ester, or a prodrug thereof; and a pharmaceutically acceptable carrier; provided that the compound is not apicularen A or B.

19. (Previously Presented) The composition of claim 18, wherein said compound is selected from the group consisting of:



(IG)

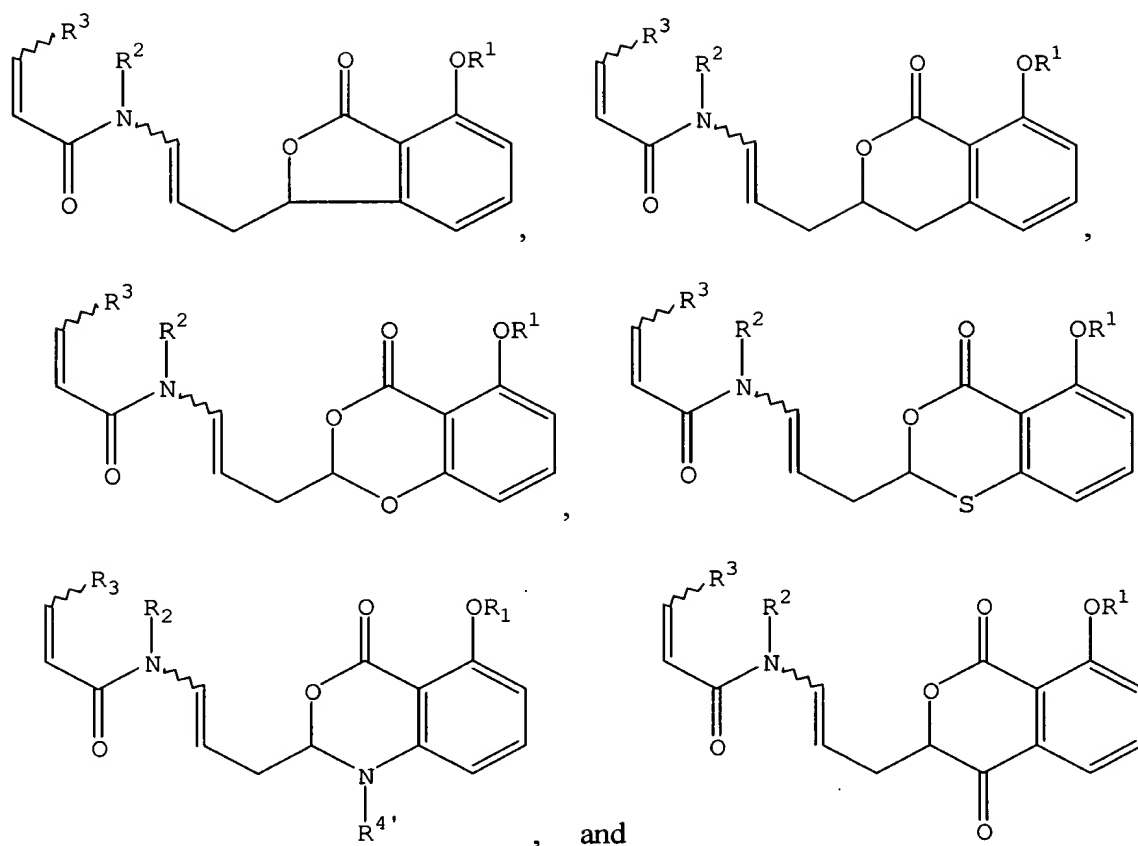


and

(IH),

wherein  $R^1$ - $R^3$  are as defined in claim 18; A is a covalent bond or a  $C_1$ - $C_6$  straight-chain saturated or unsaturated alkyl linker which is unsubstituted or is substituted with a one or more substituents selected from the group consisting of a halogen, a nitro, an amino, a hydroxyl, a thio, an acyl, an alkyl, and a cyano; X is a covalent bond or a  $C_1$ - $C_5$  straight-chain saturated or unsaturated alkyl linker which is unsubstituted or is substituted with a one or more substituents selected from the group consisting of a halogen, a nitro, an amino, a hydroxyl, a thio, an acyl, an alkyl, and a cyano; and W is O, S, C(O), C(S),  $S(O)_n$  or  $N-R^{4'}$ , wherein  $R^{4'}$  is H, a straight-chain or branched saturated or unsaturated alkyl, an aryl,  $R^6CH_2$ -,  $R^6CO$ -, or  $R^6SO_2$ -, wherein  $R^6$  is as defined in claim 18 and n is an integer from 0-2.

20. (Previously Presented) The composition of claim 19, wherein said compound is selected from the group consisting of:



21. (Previously Presented) The composition of claim 18, which further comprises a vacuolar-type (H<sup>+</sup>)-ATPase inhibiting effective amount of at least one additional compound other than a compound defined in claim 18.

22. (Previously Presented) The composition of claim 21, wherein said additional compound is selected from the group consisting of bafilomycins and concanamycins.

23. (Previously Presented) The composition of claim 22, wherein said additional compound is concanamycin A.

24. (Previously Presented) The composition of claim 22, wherein said additional compound is bafilomycin A<sub>1</sub>.

25. (Previously Presented) The composition of claim 18, wherein said vacuolar-type (H<sup>+</sup>)-ATPase inhibiting-effective amount is effective to inhibit intra-organellar acidification of intracellular organelles.

26. (Previously Presented) The composition of claim 18, wherein said vacuolar-type (H<sup>+</sup>)-ATPase inhibiting-effective amount is effective to inhibit urinary acidification.

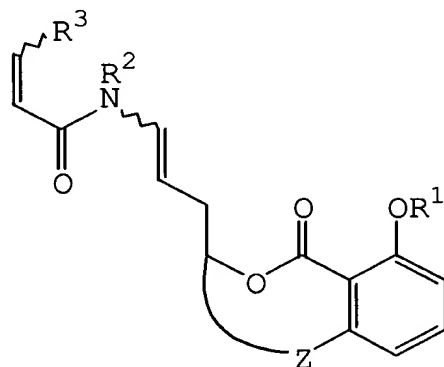
27. (Previously Presented) The composition of claim 18, wherein said vacuolar-type (H<sup>+</sup>)-ATPase inhibiting-effective amount is effective to inhibit bone resorption.

28. (Previously Presented) The composition of claim 27, wherein said vacuolar-type (H<sup>+</sup>)-ATPase inhibiting-effective amount is effective to treat osteoporosis.

29. (Previously Presented) The composition of claim 18, wherein said vacuolar-type (H<sup>+</sup>)-ATPase inhibiting-effective amount is effective to inhibit fertility.

30. (Previously Presented) The composition of claim 18, wherein said vacuolar-type (H<sup>+</sup>)-ATPase inhibiting-effective amount is effective to inhibit angiogenesis.

31. (Currently Amended) A method of treating ~~or preventing a~~ an intra-organellar acidification of intracellular organelles ~~condition treatable~~ by the inhibition of vacuolar-type (H<sup>+</sup>)-ATPase, said method comprising administering to a patient an amount effective to treat intra-organellar acidification of intracellular organelles of a vacuolar-type (H<sup>+</sup>)-ATPase ~~inhibiting-effective amount~~ of at least one compound of the formula:



(I),

wherein  $R^1$  and  $R^2$  are the same or different and each is H, a straight-chain or branched saturated or unsaturated alkyl, an aryl,  $R^6CH_2-$ ,  $R^6CO-$ , or  $R^6SO_2-$ , wherein  $R^6$  is H, a straight-chain or branched saturated or unsaturated alkyl, or an aryl;  $R^3$  is H, a straight-chain or branched saturated or unsaturated alkyl, an aryl, an oxime, or an oxime methyl ether; the aromatic ring is unsubstituted or substituted with at least one substituent selected from the group consisting of a halogen, a nitro, an amino, a hydroxyl, a thio, an acyl, an alkyl, and a cyano; the saturated alkyl, unsaturated alkyl and aryl substituents defined in  $R^1$ - $R^3$  and  $R^6$  are unsubstituted or substituted with at least one substituent selected from the group consisting of a halogen, a nitro, an amino, a hydroxyl, a thio, an acyl, an alkyl, and a cyano; and Z is a contiguous linker comprising a chain of 0-6 atoms which, together with the five atoms beginning with the carbon of the aromatic ring in meta-relationship with  $OR^1$  of formula (I) and ending with the carbon directly attached to the alkyl oxygen of the lactone of formula (I), said carbons being covalently bonded to either end of linker Z, integrally form a 5-11 membered ring; or a pharmaceutically acceptable salt, an ester, or a prodrug thereof, provided that the compound is not apicularen A or B.